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Drahos, Jennifer; Boateng-Kuffour, Adriana; Calvert, Melanie; Levine, Laurice; Dongha, Neelam ; Li, Nanxin; Pakbaz, Zahra; Shah, Farrukh; Martin, Antony P.

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ORIGINAL RESEARCH ARTICLE

Health-Related Quality-of-Life Impacts Associated with Transfusion-Dependent β-Thalassemia in the USA and UK: A Qualitative Assessment

Jennifer Drahos[1] · Adriana Boateng-Kuffour[1] · Melanie Calvert[2,3,4,5] · Laurice Levine[6] · Neelam Dongha[7] · Nanxin Li[1] · Zahra Pakbaz[8] · Farrukh Shah[9] · Antony P. Martin[10]

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Abstract

Background Individuals living with transfusion-dependent β-thalassemia (TDT) experience reduced health-related quality of life due to fatigue and chronic pain, which cause disruptions to daily life. Currently, limited qualitative data exist that describe these impacts.

Objective This study aimed to examine the ways in which symptoms and current treatments of TDT impact health-related quality of life, to holistically describe the humanistic burden of TDT, and to identify the unmet needs of individuals living with TDT.

Methods Adults (aged ≥ 18 years) with TDT and caregivers of adolescents (aged 12−17 years) with TDT participated in semi-structured one-on-one virtual interviews and focus group discussions. Interviews were conducted in the USA and UK and lasted approximately 60 minutes. After transcription, the interviews were analyzed thematically using a framework approach.

Results A total of ten interviews/focus group discussions (six interviews and four focus group discussions) were conducted with 14 adults with TDT and two caregivers of adolescents with TDT. A framework analysis revealed five themes describing health-related quality of life (negative impacts on daily activities, social life, family life, work and education, and psychological well-being) and three themes describing the lived experience of TDT (impact of red blood cell transfusions and iron chelation therapy, treatment, and stigma). Physical, psychological, and treatment-related factors contributed to negative impacts on daily activities, social and family life, and work and education. Concerns about reduced lifespan, relationships and family planning, and financial independence were detrimental to participants' mental well-being. Participants reported having high resilience to the many physical and psychological challenges of living with TDT. A lack of TDT-specific knowledge among healthcare professionals, particularly regarding chronic pain associated with the disease, left some participants feeling ignored or undermined. Additionally, many participants experienced stigma and were reluctant to disclose their disease to others.

Conclusions Individuals living with TDT experience substantial negative impacts on health-related quality of life that disrupt their daily lives, disruptions that are intensified by inadequate healthcare interactions, demanding treatment schedules, and stigma. Our study highlights the unmet needs of individuals living with TDT, especially for alternative treatments that reduce or eliminate the need for red blood cell transfusions and iron chelation therapy.

1 Background

β-thalassemia is a hereditary hemoglobinopathy diagnosed in over 40,000 newborns worldwide each year, approximately 25,500 of whom have transfusion-dependent β-thalassemia (TDT) [1, 2]. In England, approximately 26 newborns had confirmed β-thalassemia between 1 April, 2016, and 1 March, 2017, and approximately 1300 individuals are currently affected by TDT [3, 4]. In the USA, the prevalence of β-thalassemia is poorly documented and underestimated, but it likely affects at least 2600 individuals [5]. In β-thalassemia, mutations in the β-globin gene (HBB) lead to reduced or absent production of β-chains of adult hemoglobin and contribute to ineffective erythropoiesis and chronic anemia [6]. β-Thalassemia is a progressive disease associated with the development of multiple clinical complications, including in the skeletal, hepatic, endocrine, and cardiovascular systems [7].

Extended author information available on the last page of the article

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Key Points for Decision Makers

There are limited qualitative data describing the effect of reduced health-related quality of life on the lived experiences and unmet needs of individuals with transfusion-dependent β-thalassemia.

Insights from 14 adults with transfusion-dependent β-thalassemia and two caregivers in the USA and UK revealed significant disruptions to daily life. Key affected areas included social, family, work, and educational activities, as well as mental well-being.

These negative impacts were amplified by a lack of knowledge of transfusion-dependent β-thalassemia among healthcare professionals, treatment-related burden on time and finances, and stigma.

Individuals living with TDT, the most severe form of β-thalassemia, rely on regular, lifelong, red blood cell transfusions (RBCTs) for survival and require iron chelation therapy (ICT) to mitigate the toxicities associated with a transfusion-related iron overload, which may affect the endocrine system (e.g., hypogonadism, hypothyroidism, and osteoporosis), heart, liver, and lungs [8]. The burden of TDT and the frequency and invasiveness of its treatments can negatively impact health-related quality of life (HRQoL) [9, 10].

Previous studies have reported reduced HRQoL in individuals living with TDT, with impairments identified across physical, psychological, and social functioning [10–13]. The pain and fatigue commonly experienced by individuals living with TDT, along with the time required to manage the disease, have been identified as major contributors to their reduced HRQoL [12]. Moreover, TDT and its management can negatively affect educational attainment, employment, and finances [10, 13, 14].

New gene therapies on the horizon have the potential to dramatically change the course of TDT and treatment experience for individuals living with this disease [15, 16]. Unlike RBCTs and ICT, gene therapies can target the underlying genetic cause of the disease and can significantly reduce or eliminate the need for lifelong treatments. Research is needed to establish a baseline for HRQoL in TDT, thereby providing a reference to assess the impact of new therapies. Although some studies have reported the quantitative effects of TDT on HRQoL [10, 12, 14], none has comprehensively assessed HRQoL or provided longitudinal patient-reported outcome data collection across the RBCT cycle. In addition, there is a paucity of contemporary data on the disease trajectory of TDT in the context of recent treatment advancements. Furthermore, there are limited qualitative data describing the lived experiences of individuals with TDT, which may identify important nuances and aspects of the lived experience that have not been well captured through existing measures. Therefore, the objective of this study was to examine the ways in which the symptoms and current treatments of TDT impact HRQoL, to holistically describe the humanistic burden of TDT, and to identify the associated unmet needs based on the perspective of individuals living with TDT.

2 Methods

2.1 Study Design and Data Source

A conceptual framework and a moderation guide for semi-structured one-on-one interviews and focus group discussions (both referred to hereafter as "interview sessions") were developed using the findings from the targeted literature review (Table 1 of the Electronic Supplementary Material [ESM]). The guide was pilot tested with a lay audience. The literature review was designed to identify relevant components of the symptomatic experiences of individuals living with TDT, including the disease burden, treatment experience, symptoms, and impacts on their HRQoL. Prior to the interviews, the interviewers familiarized themselves with the research topic during the targeted literature review phase and through discussions with the wider research team composed of patient advocates, clinicians, and methodologists. Additional training on interview approaches were provided alongside further piloting of the moderation guide.

Interview sessions were then conducted to explore the relationship between the symptomatic experiences of TDT and HRQoL. Adults living with TDT (aged ≥ 18 years) and/or caregivers of adolescents (aged 12−17 years) living with TDT were recruited to participate by patient advocacy groups (i.e., Cooley's Anemia Foundation in the USA and the UK Thalassaemia Society in the UK) [17, 18]. Participants were members of either respective patient advocacy group. Individuals or caregivers were excluded if the individual with TDT had received a hematopoietic stem cell transplant or gene therapy at any point in their medical history. Age, sex, disease, and treatment characteristics were captured with a non-probabilistic purposive sampling approach to obtain diverse views across the study sample. Participants were contacted by e-mail before the study to schedule the interview sessions. Based on participants' availability, interview sessions were conducted as either one-on-one interviews or focus group discussions.

The sessions took place virtually in a setting of the participants' choosing, and although participants were asked to join the interview sessions alone, some individuals may have participated in the presence of non-participants (e.g., a family member if they participated at home). Interview sessions were conducted by Antony P. Martin and Joseph Jones. Although transcripts were not shared, participants were invited by e-mail to provide clarification or feedback on the findings from their interview session (i.e., "member checking"). All interview sessions were completed between January and February 2022.

2.2 Qualitative Analyses

All interview sessions were audio recorded, transcribed, documented by field notes, reviewed, and reported qualitatively. Data were organized by theme using NVivo 12 (Lumivero, Denver, CO, USA) and analyzed thematically using the Framework Method [19].

Themes included in the moderation guide and patterns identified in the interview transcripts were used to create deductive and inductive codes, respectively. The first three transcripts were coded independently by two researchers and compared. Intercoder reliability was assessed, and the analysis team discussed and resolved any coding discrepancies.

A "coding tree" was developed based on the deductive and inductive codes and applied to all transcripts through the NVivo 12 software so that sections of the transcripts were classified under the respective code. Each transcript was reviewed and coded independently by two researchers. Data were interpreted and summarized by code, and individual exemplar quotes were selected for clarification. Data saturation was assessed to determine the number of interview sessions after which no new topics, opinions, or views were gathered (Tables 2a and b of the ESM). The reporting of methods and results for this study adhere to the Consolidated Criteria for Reporting Qualitative Research and the National Institute for Health and Care Excellence methodology checklist for qualitative studies [20, 21] (Tables 3 and 4 of the ESM).

2.3 Participant Demographics and Study Outcomes

Demographics (i.e., age, sex, and geography) and self-reported clinical characteristics, including type of TDT, age at diagnosis, treatment characteristics, and number of RBCTs in the past 0−12 months and past 12−24 months, were evaluated at enrollment and presented descriptively. Data on the symptomatic experiences of TDT and its impact on HRQoL were reported qualitatively. Interview or focus group discussion outcomes are reported by the number of interview sessions, where "many" refers to three or more sessions and "most" refers to six or more. Exemplar quotes are presented alongside the participant's age category, sex, and country of residence, as well as information on the interview session and setting in which the quote was obtained.

2.4 Ethics

This study was performed in accordance with the ethical standards of the institutional and/or national research committees, the 1964 Helsinki Declaration and its later amendments, and the codes of conduct of the Association of the British Pharmaceutical Industry, British Healthcare Business Intelligence Association, and European Pharmaceutical Market Research Association [22–24].

This study was reviewed by the WIRB-Copernicus Group® Institutional Review Board and granted an exemption because of 45 CFR § 46.104(d)(2). All participants provided informed consent and were compensated with a voucher to an online retailer.

3 Results

3.1 Participant Demographics and Self-Reported Clinical Characteristics

Overall, 16 participants were included in the study: 14 were adults (aged ≥ 18 years) living with TDT and two were caregivers of adolescents (aged 12−17 years) living with TDT (Table 1). Approximately four individuals initially signed up but did not provide a further response (for unknown reasons). The age of participants varied broadly (mean = 37.2 years; standard deviation = 14.3), though the number of male and female participants was balanced. Most participants lived in the UK ($n = 9$) and had received ≥12 RBCTs in the past 0−12 months and past 12−24 months (Table 1).

3.2 HRQoL Impacts

Overall, ten interview sessions (six interviews and four focus group discussions, with no repeat sessions) were conducted, and data saturation was reached following completion of the first seven sessions (Tables 2a and b of the ESM). Eight key themes were identified in these sessions, including five that described the negative effects of TDT on HRQoL and three that described the lived experience of TDT (Fig. 1). These themes are discussed below, and exemplar quotations are reported in Table 2.

3.2.1 Daily Activities

In seven interview sessions, participants reported that TDT affected their ability to complete daily activities, including household chores, shopping for groceries, engaging in physical activity, climbing stairs, and showering. Some participants more than others experienced more frequent and intense disruptions to daily activities, citing fatigue and pain as the most common cause of the disruptions:

> "On a typical day, waking up in the morning, my entire being, it just feels tired […] So you're never really 100%. You have aches and pains that are constant, but it's part of your being." Participant living with TDT, aged > 50 years, male, UK (Interview 7)

> "The osteoporosis the past five years has advanced so much and it's given me so much pain. Just last year within a few months, October and December, I had two fractures. My collarbone and my fibula. I'm on now temporary disability until my fibula heals properly. It's discouraging that I'm still super smart, I'm super savvy, and I have to just constantly think about I can't walk that much. I can't even go down the subway stairs. It's discouraging that this is what stops me, not thalassemia." Participant living with TDT, aged > 50 years, female, USA (Interview 9)

Daily activities were impacted by the cyclic nature of RBCTs. Participants reported feeling especially tired in the days to weeks leading up to an RBCT, groggy or depleted on the day of an RBCT, and energized in the weeks following an RBCT. In six interview sessions, participants reported issues with concentration in the weeks leading up to an RBCT. The inability to focus decreased their work productivity and educational attainment. One participant described having "brain fog" that reduced their capacity to think things through and caused verbal disorder when speaking. Another participant described having "clouded judgment" and said that they could not manage on their own as a result.

3.2.2 Social Life

The negative impacts of TDT on social life were discussed in seven interview sessions. Fatigue was often mentioned as a barrier to socialization:

> "I always make excuses. The motivations are there but I don't feel like I have the energy to just go." Participant living with TDT, aged 18–35 years, female, UK (Interview 2)

One participant shared that they were unable to engage in and sustain meaningful friendships because they were frequently unable to attend social occasions. Another participant mentioned that they had to choose between working or having a social life because their low energy levels did not allow them to sustain both.

Complications related to TDT were cited as impacting social life as well; one participant had led an active social and travel life until pain caused by osteoporosis and bone fractures had rendered them unable to continue. Isolation and stigma (e.g., being perceived as "different," feeling like an "outcast," and "not fitting in anywhere") were also mentioned by some participants as barriers to social interaction.

Participants in eight interview sessions discussed the difficulties of talking to others about their disease. Some

Table 1 Participant characteristics ($N = 16$)[a]

Participant characteristics	*n* (%)
Sex	
Female	8 (50.0)
Male	8 (50.0)
Age, years	
Mean (SD)	37.2 (14.3)
Median (range)	38.5 (12−59)
Age categories, years	
12–17	2 (12.5)
18–35	6 (37.5)
36–49	3 (18.8
> 50	5 (31.3)
Residence	
USA	7 (43.8)
UK	9 (56.3)
Age at diagnosis of TDT, years	
< 1	9 (56.3)
1–2	5 (31.3)
> 2	2 (12.5)
Frequency of RBCTs in past 0–12 months	
12–15	5 (31.3)
16–20	7 (43.8)
20–25	1 (6.3)
> 25	1 (6.3)
Unsure[b]	2 (12.5)
Frequency of RBCTs in past 12–24 months	
12–15	7 (43.8)
16–20	5 (31.3)
20–25	1 (6.3)
> 25	1 (6.3)
Unsure[b]	2 (12.5)

RBCT red blood cell transfusion, *SD* standard deviation, *TDT* transfusion-dependent β-thalassemia

[a]For adolescents with TDT (aged 12–17 years), responses were provided by their caregivers but reflect characteristics of the individuals with TDT

[b]Participants who reported being "unsure" may have experienced changes in RBCT frequency over the past 0–12 and 12–24 months

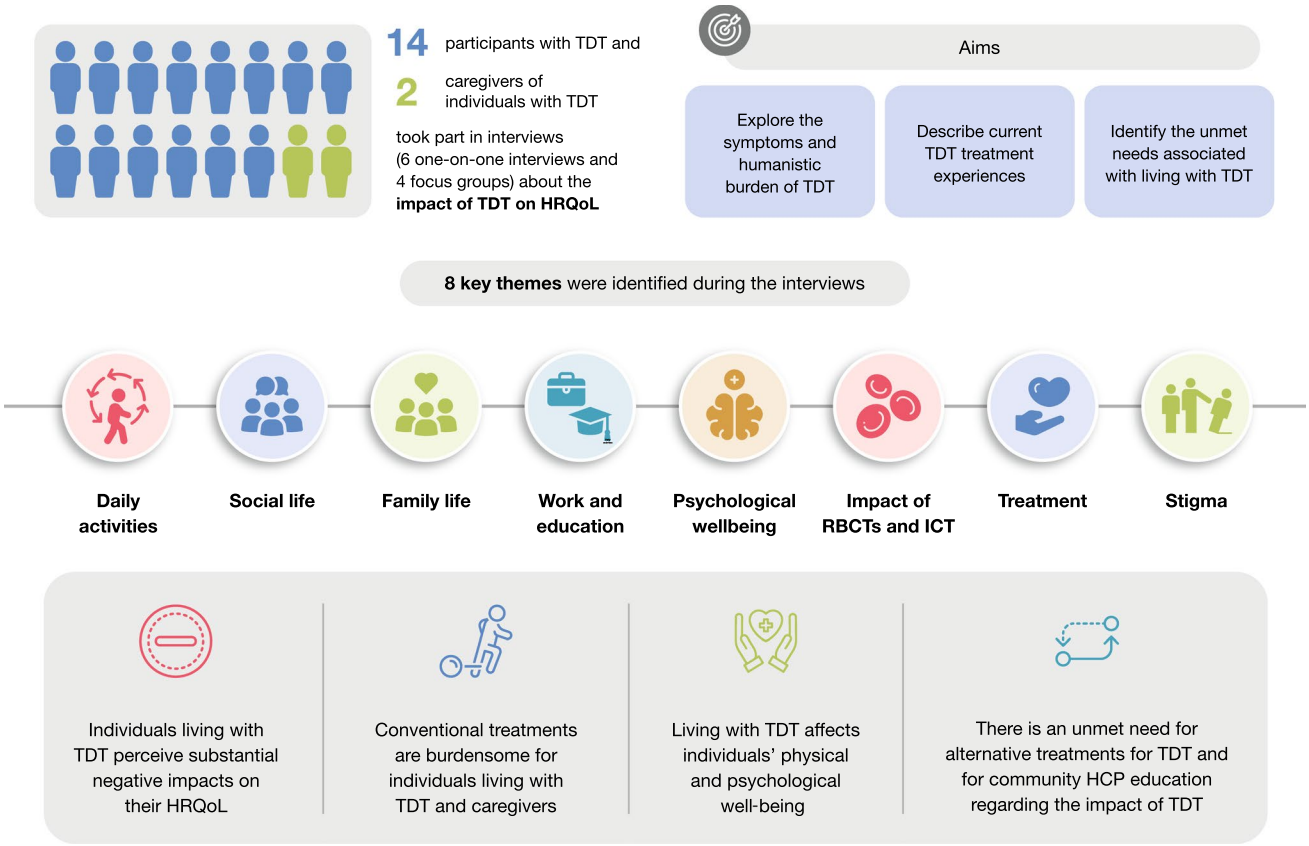

Fig. 1 Key themes identified in participant interviews. *HCP* healthcare professional, *HRQoL* health-related quality of life, *ICT* iron chelation therapy, *RBCT* red blood cell transfusion, *TDT* transfusion-dependent β-thalassemia

participants chose to freely disclose their disease to others, whereas other participants chose to conceal their disease from their social circle. Participants discussed parental influence and societal stigma as factors in deciding whether to disclose their disease to others. Communicating about TDT may present a psychological barrier in participants' lives. One participant shared that they felt psychological exhaustion from being transparent and honest about their disease, and another shared that concealing their disease from friends was difficult to manage. Some participants noted that they were hesitant to disclose their disease to others when they were children or young adults but that they were more open to do so as adults.

3.2.3 Family Life

The burden on TDT burden on family life was discussed in seven interview sessions:

> "That's the biggest thing as well; it affects everybody. It affects everybody, you don't realize it. One of the things that I've tried to avoid, I do have children thank God, and they are grown up now, but because of my illness, I didn't want them to think any less of their father." Participant living with TDT, aged > 50 years, male, USA (Interview 7)

Participants mentioned the time sacrificed by family members for their treatment and healthcare and the mental toll of these efforts, especially on family members caring for adolescents with TDT. One participant noted that their mother managed their appointments, medications, and at-home injections, and felt that these responsibilities had a negative psychological impact on their mother. Participants often reported withdrawing from family activities because of their disease, which is especially difficult for participants with children. Family dynamics may also be affected by TDT. One participant felt that the amount of attention they received because of their disease caused their siblings to resent them, and another felt that they were not given the independence they desired because of their family "shouldering responsibility" for their disease. Parental guilt and self-blame owing to the hereditary nature of TDT were also discussed. However, some participants reported positive effects of TDT on family life. For example, one participant

Table 2 Exemplar quotes depicting themes and sub-themes identified during interviews with participants (or their caregivers) living with TDT to describe the impacts of the disease on HRQoL

Themes	Sub-themes	Exemplar quotes
Daily activities	Disruption to day-to-day activities	"I guess as a male and having a wife and family and children, it impacts me a lot. I used to be able to cut the grass and stuff like that. Going back probably in my thirties, I came in from cutting the grass and I was ready to pass out. My wife was like you're not doing that anymore. I'm like, what do you mean? I love to do it. It's something I like to do. She's like you just can't handle it anymore. We hired somebody to [cut the] grass." Interview 9, Individual 1 (aged > 50 years, male), USA
		"I can do like cleaning and I clean my room, play with my children and stuff, but when it comes to harder work like cooking or standing for a little bit, over half an hour, it's like straightaway I have leg pains and I can't do them." Interview 2, Individual 1 (aged 18−35 years, female), UK
	Maintaining an active lifestyle	"If I went on a little bike ride with my son I'd be out of breath and I'd say, 'I can't go any further son,' and he'd say, 'Dad you need to go here,' and I said, 'Well, let's jump in the car and go." Interview 8, Individual 2 (aged > 50 years, male), UK
		"I do some light exercises that's been suggested by the doctor such as yoga but nothing like high impact. Even though it's supposed to be quite good but I don't have the energy for it." Interview 1, Individual 2 (aged 18−35 years, female), UK
Social life	Difficulty communicating about condition	"But as I got older though, I became less sort of nervous about telling friends, because then it just became – my relationship with thalassemia changed. You know, this is just something that's a part of me now, and I think friends aren't going to look at me any differently once I tell them, whereas I didn't really believe that when I was a kid, nor did I understand it." – Interview 10, Individual 2 (aged 36−49 years, female), USA
		"Social life, you know, it made it a little bit more difficult, because, you know, I made the decision early on that I wasn't going to tell anyone in my circle of friends, even good friends, because I didn't want to be different than everyone else. And so, I decided that, you know, I wouldn't tell people about it. So, trying to hide it, right, that made it a little ore difficult, you know, difficult to manage it in the social circle of friends and stuff like that." Interview 10, Individual 2 (aged 36−49 years, female), USA
	Impact on social life	"I think I am antisocial because I really find reasons to not go out, so if a friend says, 'Oh why not come for dinner or lunch? I always make excuses. I'm not antisocial in personal, I like life, and I like to go out, but obviously the … Again, the motivations are there but obviously I don't feel like I have the energy to just go." Interview 2, Individual 1 (aged 18−35 years, female), UK
		"When you're tired, your mood kind of is quite low. You're not really wanting to do anything for like I just sit there at school with my friends at lunch but just not talk to them." Interview 1, Individual 2 (aged 18−35 years, female), UK
Family life	Burden on family	"That's the biggest issue with me is thinking I'm a burden on my family or on the world, like getting blood and – you know, so working through that – because I was treated like a burden mainly, and told I was, so it's kind of a hard message to erase." Interview 10, Individual 2 (aged 36−49 years, female), USA
		"I do get a lot of help from my sister who lives across the street, and my brother who lives downstairs, and my mum and grandma who live across town. So, if I genuinely don't feel up to cooking, if I call the right one, they might bring me food. But there is a lot of things, if I really need help, I can just call my mum or my grandma, they will help me, come and do the laundry, or whatever may need to be done, cleaning the house if my nurse is not available." Interview 4, Individual 1 (aged 18−35 years, female), USA

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
	Pity from friends or family	"They made me feel very small growing up. I always felt like this weight of pity from them." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Romantic relationships	"I grew up thinking I would never want to bring another child into this world that has what I have." Interview 4, Individual 1 (aged 18−35 years, female), USA "It makes relationships a little bit harder, unless it is something you are just open about and then you start off as friends. You know, it is a little bit easier that way, but it varies from person to person. It can be a problem." Interview 6, Individual 1 (aged 18−35 years, male), USA
Work and education	Effect on school	"They just wanted me out [of high school] because they didn't have a nurse, they didn't have anyone who actually knew what they were doing when it came to medical devices." Interview 6, Individual 1 (aged 18−35 years, male), USA "When I was in school I had a go-stop-go-stop because I would get sick or, you know, like I would have to be in the hospital or like the schedule wouldn't match up." Interview 3, Individual 1 (aged 18−35 years, female), USA
	Missed time from school	"I do miss school every like, every four weeks on a Wednesday but luckily that is only one lesson but it is the same subject, which obviously I'm sitting my A levels in May, June so like I think it does add up quite a bit." Interview 1, Individual 2 (aged 18−35 years, female), UK
	Work impact	"At work it gets really hard to focus. I just want to go home and sleep. After work I don't feel like doing anything and I just want to sleep." Interview 4, Individual 1 (aged 18−35 years, female), USA "And it worries me a lot because, you know, some jobs, you know, they're not really flexible with things like that and finding a job that'll pay well and have good insurance and, you know, is flexible about time, knowing that I might get sick here or there or … you know, I can't really control that. So it's just very difficult and it's stressful like overwhelming to think about that." Interview 3, Individual 1 (aged 18−35 years, female), USA
	Being treated differently at work	"That flexibility comes at a cost and it's one of the reasons why I've left is it made it really hard to kind of be seen as a normal employee or as capable as employee." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Trying to match peers	"I used to always say, 'Look, if it's any comfort, I'll make the hours up. I don't want to lose out, I want to be treated as normal and I'll work the hours back up if you need to,' and there was certain jobs where I did need to do that, a couple of jobs that I did." Interview 8, Individual 2 (aged >50 years, male), UK "The only way I was able to manage it [missing work] before Covid was to work that time back. Which always led to [being] more run down." Interview 7, Individual (aged > 50 years, male), UK
	Unable to work	"We can't work, or you go through a lot of jobs because they get sick of you missing dedicated days you know, unless you schedule all your appointments around working." Interview 6, Individual 1 (aged 18−35 years, male), USA "I'd recently reduced my hours, well, I left my job in late October because physically I just, it was just too much for me. I was doing 30 hours, I'm now doing some, I'm now working in the same sort of job but just for ten hours a week." Interview 8, Individual 1 (aged > 50 years, female), UK

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
	Needing time off work	"I mean, it's like, you know, a half time job sometimes. I call it invisible work." Interview 10, Individual 2 (aged 36−49 years, female), USA "You attend hospital for transfusion you've got to take the whole day off so then you're working the weekend instead, and vice versa." Interview 7, Individual (aged > 50 years, male), UK
	Insurance concerns	"It was always any time you're switching jobs you were always cautious because you didn't want the other job to find … I mean with anybody, but more so us because if there was any type of gap we lose healthcare and we're not getting it back. It takes a lot to get it back." Interview 9, Individual 1 (aged >50 years, male), USA "Like they [adolescents] can't just start their own small business, you know. Financially, they wouldn't be able to do that. It's like a lot of small companies wouldn't be able to cover the insurance on a patient with thalassemia." Interview 10, Caregiver 1 (aged 12−17 years, female), USA
	Communication about condition at work	"I feel like that more now this last month interviewing for jobs. I definitely didn't want to say anything about it. I don't want people to think that because I have some sort of chronic disease that I wouldn't work as fast or as hard as someone else for sure." Interview 4, Individual 1 (aged 18−35 years, female), USA
Psychological well-being	Ability to concentrate	"The brain itself, I feel as though it's, the capacity has gone down to think things through, to say stuff, you know, I'm always like sometimes mixing my words and it's so grateful to receive that transfusion and to just stand back up and think oh, I feel alive again, you know." Interview 8, Individual 2 (aged > 50 years, male), UK "I do notice it and kind of I'm more clumsy leading up to that sort of thing. I can't get my words out sometimes; I can't express myself." Interview 8, Individual 1 (aged > 50 years, female), UK
	Anxiety	"General worrying about things much greater than you constantly. Interview 4, Individual 1 (aged 18−35 years, female), USA "Dread of the ferritin going too high and then trying to bring it back down to an acceptable level." Interview 1, Individual 1 (aged 18−35 years, male), UK "Anxiety about not being able to catch up and missing so much school because I'm not there." Interview 1, Individual 2 (aged 18−35 years, female), UK
	Concerns about future	"I'm constantly worried about retirement and then also we're worried that I'm not even going to be old enough to retire, so fighting there." Interview 4, Individual 1 (aged 18−35 years, female), USA "That was our mentality when we were that young. We weren't planning on retiring." Interview 9, Individual 1 (aged > 50 years, male), USA
	Denial of condition	"I was transitioning out of paediatric care into adult care, so it was a little over a year. But during that transition it was just very bad. I was in denial that I had thalassemia, so I wasn't taking my medications." Interview 4, Individual 1 (aged 18−35 years, female), USA "It made me want to pretend that it wasn't an issue at all, that I didn't have it. That I wasn't a girl who had to take medications every day or go and get blood transfusions, so I did it. That's what I mean, yes, it's easy to forget taking a pill and there are tricks that you can do to remember. But if it's a deeper psychological thing where I would rather just pretend that it didn't exist anymore, it's harder." Interview 4, Individual 1 (aged 18−35 years, female), USA

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
	Depression and low mood	"You don't think of yourself as being really capable or being able to be successful in doing anything. So that's been a constant struggle throughout my life." Interview 7, Individual (aged > 50 years, male), UK "Depression was always something I fought. Thank god I was able to talk to my friends and get through it." Interview 9, Individual 1 (aged >50 years, male), Individual 2 (aged > 50 years, female), USA
	Isolation	"I just feel like sometimes I'm like an outcast because it's so rare for me to have it." Interview 3, Individual 1 (aged 18−35 years, female), USA "'Do I fit in here? No, not really. Do I fit in here? No, not really.' I don't look like anything's wrong with me, but inside I have a lot of things that are wrong with me." Interview 3, Individual 1 (aged 18−35 years, female), USA
	High resilience	"We don't know our limits. We are so into survival and pushing and being a warrior that we always push past out limits." Interview 9, Individual 2 (aged > 50 years, male), USA "We're not ones that sit back and try and let thalassemia define us. Our body does tell us when to stop. Sometimes you miss out on things. We're still here fighting away." Interview 9, Individual 2 (aged > 50 years, female), USA
	Irritability	"Leading up to a transfusion I usually am a little bit more tired, sluggish, way more irritable." Interview 6, Individual 1 (aged 18−35 years, male), USA "There are some bad days when my mood is really low and irritable, and sometimes I really don't know why it's happening also, and understanding is really difficult like why I'm feeling this way." Interview 2, Individual 1 (aged 18−35 years, female), UK
	Mood swings	"Sometimes your mood changes I think definitely because when you're tired, your mood kind of is quite low." Interview 1, Individual 2 (aged 18−35 years, female), UK "The biggest thing for me was mood swings because I wasn't getting transfused and I didn't know why I would go into these like … I would be almost manic." Interview 9, Individual 1 (aged > 50 years, male), USA
	Growth and weight	"Going to the paediatric hematologist and just being told she's short because of thalassemia or she's possibly short because of thalassemia was hard to hear. I'm like, gosh, darn it, I have this which already makes me do all of this and it's making me short." Interview 4, Individual 1 (aged 18−35 years, female), USA "I'm pretty short myself and have been since I was a kid. I was always the shortest in my class, and so that gave me a little bit of stigma, until I shook that off, you know, when I became an adult." Interview 10, Individual 2 (aged 36−49 years, female), USA
	Mourning members of the community	"I've never been afraid of death. That was one of my big things. I knew I was dying. At a very young age I knew I was dying and I saw so many of my friends that passed away at 19 and 18 and twenties. There was one clinic you could go to and see who was still left or how passed away this time. Because I wasn't going every two weeks, I was going every two months, it would be like where's Jan or where's George or where's Danny? They'd be gone." Interview 9, Individual 1 (aged > 50 years, male), USA
	Trauma	"My 29 years of having thalassemia, it's an up and down thing. It's a lot of trauma. From a young age just being in the hospital seeing this and that and growing up trying to juggle between a lot of stuff in life and top of this your health, like it gets very overwhelming, very stressful." Interview 3, Individual 1 (aged 18−35 years, female), USA

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
Impact of RBCTs	Burden of transfusions	"[…] it is tedious at times […] the feeling of going back and forth, going back for a draw and then going back the next day for a transfusion, you know? And then it's just like going up there back and forth … especially if don't live close." Interview 3, Individual 1 (aged 18−35 years, female), USA
	Iron-induced complications	"It led to the iron actually trying to escape and eating at my teeth, so they therefore did some reconstruction surgery, pulled my teeth out, and I got a pair of dentures that are on the counter like your grandpa's in the bathroom." Interview 6, Individual 1 (aged 18−35 years, male), USA "I was using a cane just to walk around, or even a walker, or at times a wheelchair." Interview 6, Individual 1 (aged 18−35 years, male), USA
	Planning around transfusions	"So I think that's one kind of general life limitation, not that it's impossible but it's just an extra hurdle and especially if, you know, some people go travelling for a couple months, I can't do that." Interview 1, Individual 2 (aged 18−35 years, female), UK "If I do anything I just need to check my diary first, I need to check my calendar first, 'Okay, what am I doing tomorrow, is there any appointment, is there anything …?' So yes, priorities when having this condition change so nowadays it's always my clinical hospital appointments, and it makes it very hard." Interview 2, Individual 1 (aged 18−35 years, female), UK
	Positive effects of transfusions	"Sometimes you may only get three or four days of raw energy, maybe a week, maybe seven days and a couple of hours. It all depends." Interview 6, Individual 1 (aged 18−35 years, male), USA
	Transfusion complications	"In my adult life I did have one where my body basically rejected the blood. I broke out in hives. They put me on steroids and antihistamines and kept me overnight. That was the biggest complication and now I think you're just getting older. I can't tolerate just the copious amounts of [food] they're putting in me." Interview 4, Individual 1 (aged 18−35 years, female), USA "One led to a nosebleed for twelve hours." Interview 6, Individual 1 (aged 18−35 years, male), USA
	Transfusion side effects	"It hasn't got to the point where I need medication, but I definitely notice some swelling or bloating after some transfusions." Interview 4, Individual 1 (aged 18−35 years, female), USA "Using the veins again and again to put a canula in can be quite difficult because he's, because of those 16 years so far that those veins have been used time and time again." Interview 1, Caregiver 1 (aged 12−17 years, male), UK
Treatment	Compliance	"My ferritin often goes high and that's because I am not the best at taking my medications every day." Interview 4, Individual 1 (aged 18−35 years, female), USA "I was having to go in [hospital] up to three times a week to get the infusion of the chelator because I wasn't taking my medication at home. I think that just made it even worse. It was a spiral and it was really bad. That really affected schooling, of course. It affected everything in my life." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Financial concerns	"If we have fractures we have to fight for physical therapy or acupuncture. That's incredibly costly." Interview 9, Individual 2 (aged >50 years, female), USA "Definitely travelling to and from the previous clinic I was at was very far. The one right before that was even further. Definitely a lot of time that I travel. Time is money and the gas to travel, car maintenance." Interview 4, Individual 1 (aged 18−35 years, female), USA

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
	Insurance burden	"Then you add the insurance where now you have to apply for yourself. You have to figure out where that's all come from and how you're going to pay for it." Interview 4, Individual 1 (aged 18−35 years, female), USA
		"Even insurance, just the amount of time that I've been on the phone or having to drive from one building to another for just to sort out my insurance has been a lot that I never expected when I was younger. That takes a lot of time." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Lack of understanding by medical professionals	"It's really hard to just look up hematologist and hope that they know what your condition is because most hematologists don't. That's really hard." Interview 4, Individual 1 (aged 18−35 years, female), USA
		"Because with every new clinic that you go to, every new hematologist, I'm having to explain my whole condition and this is the plan. You kind of have to become your own doctor, which is kind of crazy because you know yourself best." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Transition from pediatric to adult care	"Any transition is a very vulnerable point for me and I'm sure most patients, specifically the paediatric to adult transition care is a big one that there's a lot of studies done on it and I felt it first-hand." Interview 4, Individual 1 (aged 18−35 years, female), USA
		"Basically you go from a hospital system where everyone is incredibly friendly. They kind of baby you like you're in a children's hospital. You're typically under your parents' insurance. You're not managing or navigating any of that. If you don't take your medicines you do get a slap of the hand. Like, hey, you need to take your medications. You're guided a little bit more. Then you transition to adult care where they're adults and they treat you like an adult and they don't tell you or encourage you to take your medications if you're not. They just let you know what is going on. Hey, you're not taking your medication. Your iron is high. This is bad. It's very overwhelming to hear that as someone who was just a kid, I guess, a couple of months ago. Then you add the insurance where now you have to apply for yourself. You have to figure out where that's all come from and how you're going to pay for it." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Planning around treatment	"Your weekends where instead of having a break from normal stuff, you've got to spend it at the oncology clinic." Interview 6, Individual 1 (aged 18−35 years, male), USA
		"I think the other thing that is grander of scale is I could never imagine myself moving out of the country. I've thought about it a couple of times, but I don't know how I would even begin to establish care outside of a country and trust their blood washing protocol and all of that stuff. That in a way is limiting, but it's not a thing that I think about every day. Just once in a while like I couldn't easily move to another country as easily as my partner or someone like that." Interview 4, Individual 1 (aged 18−35 years, female), USA
	Time sacrifice	"Then also my transfusions, they do take a while, especially when you're new to a clinic. It's just a lot of time. It really takes the whole day away. I can't just move things around on the same day for it usually." Interview 4, Individual 1 (aged 18−35 years, female), USA
		"Oh my god, the time we sacrificed in our lives to stay healthy, we're never going to get it back but it's an investment." Interview 9, Individual 2 (aged > 50 years, female), USA

Table 2 (continued)

Themes	Sub-themes	Exemplar quotes
	Treatment side effects	"I experienced a lot of symptoms related to that [chelator], like soreness in the stomach, skin rashes, like bumps, things like that, so a lot of pain sort of generally in the stomach area all the time." Interview 10, Individual 1 (aged 36−49 years, male), USA
Stigma		"I still see that in the young patients as well and don't like to talk about it, they don't want their name to be mentioned anywhere that they have this condition. So personally I find it very strange because there's nothing wrong to have this condition." Interview 2, Individual 1 (aged 18−35 years, female), UK
		"I had serious body issues. I had such a horrible overbite and I was yellow. My eyes were yellow. I wasn't developing breasts like the other girls were. When I was in grade school kids used to say why do you look like that, and I just thought like what. They're like you're so funny looking. I didn't really understand that this is thalassemia. This is the facial features of thalassemia. It made me very upset." Interview 9, Individual 2 (aged > 50 years, female), USA

HRQoL health-related quality of life, *RBCT* red blood cell transfusion, *TDT* transfusion-dependent β-thalassemia

felt that because the disease impacted their entire family, it had brought them closer together.

The impact of TDT on romantic relationships was discussed, including discussions around communicating the disease to potential partners and around fertility and family planning. Some participants reported that they found it difficult to tell potential partners about their disease. One participant shared that a prior partner of theirs ended their relationship because the participant did not want to risk having a child who could have TDT. Endocrine issues (e.g., loss of period, insomnia, and hot flashes) were discussed by some participants; one participant felt that such issues placed a burden on their marriage, and another questioned their worth in their relationship. However, several participants reported that they had happy and healthy relationships despite recognizing that for other individuals with TDT the impacts of the disease were a concern in their relationships.

3.2.4 Work and Education

Participants in nine interview sessions reported a significant need for absence from work because of TDT. In half of the interview sessions ($n = 5$), participants reported that the need to request time off from work to accommodate RBCTs and medical appointments increased their absenteeism. Some participants felt anxious about requesting time off and were reluctant to do so; some reported working remotely during their RBCTs, using vacation time to attend RBCTs, or working on the weekend to compensate for time missed from work during the week. One participant reported that they frequently changed jobs because their employers did not understand their need to take time off because of TDT.

Participants in four interview sessions reported that TDT had affected their work life. The most common ways were that it prevented them from working or caused them to reduce their working hours, both of which led to feelings of stress and anxiety. Some felt that the frequency of TDT-related treatments had hindered their ability to develop their careers. Others felt that they had to work harder to match their peers' productivity ($n = 3$ interview sessions) and that working beyond normal working hours to compensate for their impaired productivity led to negative effects on their health.

Participants in three interview sessions said that they withheld or limited the amount of information they shared about their disease in the workplace. One participant who did not tell their employer about their disease had to use vacation time to attend TDT-related health appointments despite legal allowances for health-related time off. Further, participants in two interview sessions had concerns about being treated differently at work. Some participants avoided sharing their diagnosis during the hiring process, while others avoided taking time off from work despite experiencing periods of ill health.

Concerns about insurance coverage were raised in two interview sessions with participants living in the USA, who said that they based their career choices on the need for adequate insurance coverage for TDT and noted that care for TDT may present significant costs even with insurance coverage:

> "I think that's kind of why I chose the profession that I chose, so that I could always afford the care that I know I'm going to need. It is a very big expense even

with insurance." Participant living with TDT, aged 18–35 years, female, USA (Interview 4)

One participant had given up their dream of pursuing a career in entertainment, one caregiver felt that they had to work at a large company or government agency, and another caregiver said that starting a small business was not viable for an individual with TDT. Further, one caregiver expressed their concern over the uncertainty of their child transitioning out of family-provided insurance coverage.

Participants in all interview sessions discussed the impact of TDT on educational attainment; participants in four interview sessions reported missing school because of their disease (e.g., due to hospitalizations or RBCT schedules), though the recent advent of remote learning had benefited some younger participants. Low energy and mood sometimes impacted their educational experiences and social functioning. In two interview sessions, participants noted an inability to focus and cognitive difficulties, especially when approaching their next RBCT:

"Sat in lesson and not really focusing, it will go on but I'm not really processing it." Participant living with TDT, aged 18–35 years, female, UK (Interview 1; focus group)

Some participants reported feeling anxious about the need to catch up on missed school, particularly during exam periods.

3.2.5 Psychological Well-Being

Depression and low mood associated with coping with TDT as a chronic illness were widely reported among participants ($n = 9$ interview sessions):

"Having a chronic disease obviously definitely affects mental health a lot, and with mental health it's always up and down. There were phases of depression I have suffered in my young age and anxiety and I still suffer from depression at the moment." Participant living with TDT, aged 18–35 years, female, UK (Interview 2)

Two participants said that they had received medication to treat depression, which they attributed to living with TDT. Further, in five interview sessions, participants described having issues with anxiety, attributing their anxiety to many factors related to TDT (e.g., anxiety about the use of needles, previous treatment trauma, and high ferritin levels) and education (e.g., anxiety about missing school because of RBCTs). Participants in six interview sessions described feeling alone, isolated because they believed they were perceived as "different," unable to fit in with society, and as though no one understood the lived experience of TDT. For some participants, feelings of isolation were connected to poor mental health in terms of depression, low self-confidence, and low self-esteem, and in the worst case, suicidal thoughts. Further, reports of trauma associated with living with TDT were discussed in four interview sessions. Several participants reported having traumatic experiences resulting from TDT when they were children, such as spending extended periods of time in the hospital, dealing with complications or frequent illnesses associated with TDT, and learning that their disease was genetic.

Many participants expressed that they had difficulty growing and gaining/maintaining weight ($n = 6$ interview sessions). Their short stature, compared with that of their peers, had a significant negative psychological impact on them, especially when they were children. One participant described the distress they felt as a child after learning that TDT was likely the cause of their short stature. Some participants had low self-confidence as a result, and others reported experiencing stigma attached to their reduced height.

Participants in four interview sessions discussed fears about their future health status, fears that contributed to their feelings of anxiety and depression. One participant feared that they may not reach retirement age. One caregiver expressed worry about their child's future relationships and the acceptance required from a potential partner. Further, death was discussed by some participants ($n = 2$ interview sessions), particularly older participants who had outlived their friends. One participant described the psychological impact of visiting a treatment clinic and learning that their peers had died. Mourning peers manifested in poor compliance with treatment in some participants, while others noted that non-compliance among peers had resulted in severe complications and death.

Some participants described experiencing periods of denial about the intense demands that treating TDT places on them ($n = 2$ interview sessions). One participant described experiencing a deep psychological issue that caused them to pretend that they did not have TDT. Another participant described how ceasing to take medication because of denial about having the disease resulted in their having high iron levels and visiting the hospital more frequently to receive ICT, which then affected other aspects of their life, such as educational attainment.

Despite the impact of TDT on psychological health, participants in 80.0% ($n = 8$) of interview sessions felt that they had high resilience to the disease, had become accustomed to living with it, and had developed a "can-do" mentality as a result. One participant reported their determination to not allow TDT to become debilitating in their life.

3.2.6 Impact of RBCTs and ICT

The burden of treatment for TDT was discussed in nine interview sessions. Participants noted that the need for regular RBCTs negatively impacted their work, education and social life.

> "The blood transfusions are the biggest kind of disrupter to my [work and social] life." Participant living TDT, aged 18–35 years, female, UK (Interview 1; focus group)

Participants in all interview sessions had experienced acute clinical complications associated with the frequent use of RBCTs, including acute hemolytic reactions, allergic reactions (e.g., rashes and hives), and fever. For several participants, these complications had led them to alter their RBCT schedule to reduce the associated discomfort.

Further, participants in nine interview sessions reported experiencing chronic clinical complications associated with an iron overload, such as cardiovascular disease, pulmonary hypertension, endocrine diseases (e.g., osteoporosis, hypothyroidism, and hypogonadism), and liver fibrosis and cirrhosis. One participant mentioned that the pain caused by iron deposition, resulting in degenerative changes to intervertebral discs and joint cartilage, had affected their mobility to the point where they required mobility aids. Another participant described the negative psychological impact of learning of the irreversible damage to their thyroid and pancreas:

> "I had severe iron overload. Irreversible damage to my thyroid and to my pancreas. I was blown away by that. Blown away. I was so upset about those results." Participant living with TDT, aged > 50 years, female, USA (Interview 9; focus group)

In half of the interview sessions ($n = 5$), participants reported that they had improved energy levels and decreased fatigue after undergoing RBCTs. The positive effects of RBCTs were limited by the cyclic nature of the transfusion cycle, however, and the intensity of the positive effects varied. The cyclic nature of the transfusion cycle directly impacted their HRQoL in terms of social functioning and academic or work ability.

> "You get about a week to two weeks, depending on how often you get transfused, maybe a week or maybe two weeks of just straight raw energy, and then bang, a crash, and you are just back for the next one." Participant living with TDT, aged 18–35 years, male, USA (Interview 6)

Issues with compliance to treatments were also discussed in three interview sessions, with some participants stating that compliance with additional treatments was burdensome (e.g., adhering to a schedule for ICT). Reasons for non-compliance included choosing not to take medication because of being in denial over living with TDT, forgetting to take medication because of the treatment complexity, and avoiding certain types of treatments (e.g., a Desferal® pump for ICT) because of discomfort and pain. Nonadherence to ICT had resulted in a decline in health status in some participants due to iron-induced complications. The availability of oral ICT was noted for reducing the negative impact of the treatment on HRQoL. However, participants mentioned that the side effects of ICT can still be burdensome, such as feeling unwell or being unable to absorb nutrients from their diet.

> "Because chelator side effects, the lumps, the bumps, the bruises, also scar tissue, a lot of people have a lot of problems with [iron] chelation." Participant living with TDT, aged 36–49 years, female, USA (Interview 10)

Concerns around the impact of treatment on personal finances were discussed in seven interview sessions, particularly in the USA. Concerns around gaining adequate insurance coverage and the time commitment required to gain approval and reimbursement for treatment costs were raised specifically by participants in the USA.

3.2.7 Treatment

A perceived lack of understanding of TDT by healthcare professionals (HCPs) was discussed in four interview sessions. Participants described feeling ignored and not being heard by HCPs, particularly in relation to pain, where participants sometimes felt undermined. One participant felt that it was futile to report pain to HCPs because of their perceived lack of understanding of the pain associated with TDT, resorting to self-care instead:

> "That has changed a lot throughout life. Emergency-wise, I would much rather go hang out in a swamp with a bunch of gators and see what happens, than go to the emergency room, because the chances are they don't know what they're doing. If I am having a form of complication, they don't see them that often, especially not in my area." Participant living with TDT, aged 18–35 years, male, USA (Interview 6)

This presented both a physical and psychological burden for participants, who felt that they had to advocate for themselves, felt that they were treated as a "test dummy," or encountered doctors who were often unable to provide adequate care. There were suggestions that some individuals with TDT choose to manage symptoms at home to avoid hospital admission.

3.2.8 Stigma

Stigma was described in eight interview sessions as being a prominent part of living with TDT, leading participants to conceal their disease and/or to struggle to trust people and openly discuss their disease. Facial characteristics associated with TDT were more commonly reported in older participants (aged > 50 years), but several participants recalled negative experiences throughout their lives (e.g., name calling and bullying) that reduced their confidence and led to negative psychological effects:

> "Even though you're walking and you're talking like everybody else is and you're doing everything that everybody else does. But you're an invalid because you go to the hospital, you're not normal, you're not classed as normal […] you can feel that pity and you're treated as a second-class citizen in a way […] So, you don't think of yourself as being really capable or being able to be successful in doing anything. So that's been a constant struggle throughout my life." Participant living with TDT, aged > 50 years, male, USA (Interview 7)

Several participants perceived themselves as a burden or had been told that they were a burden, reflecting both their treatment by society and highlighting the stigma that individuals with TDT may experience. Fear of judgment and the implications of living with TDT dominated how participants lived their daily lives.

Participants hoped that raising awareness of TDT would lead to improved healthcare and perceptions in the community:

> "The one thing that we do have is to raise awareness and the more people that become aware, we're more likely to find solutions – even if we can't find a cure. We're more likely to find solutions that can make our lives easier." Participant living with TDT, aged 18–35 years, female, UK (Interview 2)

In addition, another participant shared:

> "We don't always know what the future holds for our boys, and so it's just a lot for them, and they don't even understand it now. So, whatever we can do, my husband and I, to just, you know, make our lives easier, better, develop better treatments, I'm always interested in learning about that and, you know, pushing those things forward." Caregiver, aged 12–17, female, USA (Interview 10)

4 Discussion

Our qualitative analysis demonstrated a clear, sustained, and unaddressed disease burden associated with living with TDT, which extends beyond the symptomatic experience to widely affect HRQoL, including daily activities, social and family life, work and education, and psychological well-being. These findings, which describe HRQoL from the perspective of individuals living with TDT, align with previous quantitative studies reporting low scores on various measures of HRQoL [10–13] and negative impacts on mental health [13] in individuals with this disease.

Participants acknowledged improvements in disease management with the regular use of RBCTs and oral ICT, consistent with the notion that these conventional treatments extend survival and improve HRQoL in individuals with TDT [2, 9, 25]. However, many participants thought these treatments were burdensome and negatively impacted aspects of their HRQoL (including physical, emotional, and social aspects of life), with some reporting that they experienced acute and chronic complications associated with these treatments and others reporting nonadherence to ICT despite knowing of the negative effects of an iron overload. Adherence to ICT is a known challenge for individuals with TDT and can become increasingly complex if new disease-related complications arise [26]. These data indicate a current unmet need for alternative treatment options that mitigate the clinical complications associated with conventional treatments; several novel gene therapies that aim to provide curative options for individuals with TDT, therapies that can eliminate the need for and consequences associated with lifelong RBCTs and ICT are currently being evaluated in clinical trials [15, 27, 28].

Participants also described experiencing temporal changes in HRQoL, which appeared to reflect the cyclic nature of RBCTs, wherein hemoglobin levels increase sharply after transfusion and decrease thereafter [29]. These temporal changes have not been well captured in quantitative studies of HRQoL. For example, participants reported feeling fatigued in the time leading up to an RBCT (i.e., which may have been linked to having lower hemoglobin levels) but more energetic immediately after an RBCT (i.e., which may have been linked to having higher hemoglobin levels). However, as hemoglobin levels likely waned in the weeks following an RBCT, many participants noted that symptoms, such as fatigue, returned. Similar results were observed in a recent analysis of patient-reported and caregiver-reported burden of TDT, with the worst levels of pain and fatigue being experienced by individuals living with TDT in the days leading up to an RBCT [12]. Given the corresponding

effects on daily activities, social and family life, and work and education, our data further emphasize the need for alternative treatment options that minimize the negative and cyclic effects on HRQoL in individuals with TDT.

Transfusion-dependent β-thalassemia has established effects on psychological well-being [13], and depression, anxiety, low mood, and isolation were all widely discussed by participants in our study as part of the burden of living with TDT. Experiencing stigma was also commonplace for them, and the resulting sense of vulnerability negatively impacted their work and education. Stigma has been reported previously in individuals with TDT, related both to the fear that disclosing their disease to others would result in possible discrimination and to the experience of actual discrimination stemming from society's erroneous perception that individuals with TDT have impaired physical characteristics and/or mental capabilities [30, 31]. Further stress was imposed by demanding treatment schedules and the financial burden of treatment, especially as it related to participants missing time at work and dealing with insurance in the US healthcare system. These observations align with those of previous studies, which linked frequent healthcare visits (e.g., for RBCTs) and time spent managing health insurance, arranging childcare, and blood matching to the burden of disease for individuals with TDT and their caregivers [10, 12].

Our data also showed that TDT had negative effects on both the individuals diagnosed with the disease and those around them, including family and prior partners with whom they were romantically involved. Participants noted the overall and time-related burdens of providing care for individuals living with TDT and the mental toll of caregiving. Caregivers of individuals with TDT in previous studies have noted the high disease burden [12], decreased HRQoL [10], and negative impacts on work [10] associated with this care. Additionally, caregivers have reported negative effects on siblings in the home environment, according to environmental domains of the World Health Organization Quality of Life Assessment (WHOQOL-BREF) measure [32].

Despite the demands of living with TDT, many participants maintained a sense of hope and an ability to cope with these demands. Many participants felt that they had high resilience to the disease, with some mentioning that they "adapted" to life with TDT. However, several participants described receiving inadequate disease management in healthcare settings, which they attributed to a perceived lack of knowledge of TDT among HCPs, making them reluctant to seek care. Participants emphasized their desire for raising awareness of TDT, which they believed would lead to improved healthcare and improved perceptions of TDT within their communities. These findings highlight the urgent need to further educate community practitioners on the impact of TDT and provide accessible care to individuals with this disease. Increasing awareness would allow individuals with TDT to advocate for improving healthcare and ameliorating the health disparities they face.

4.1 Limitations

This study had several limitations. First, although participants were asked whether the information provided to them during interview sessions was easy to comprehend, some may have felt unable to vocalize their views fully in a group setting. Moreover, in the focus group discussions, we were unable to gauge the frequency of all symptomatic and HRQoL impacts experienced by each participant. Therefore, instead of recording the symptomatic and HRQoL impacts experienced by each participant, we recorded the frequency of impacts mentioned across the ten interview sessions. Interviewers attempted to address this potential limitation by encouraging participants to share additional perspectives via e-mail after completion of the interview sessions. Second, patient advocacy groups were used to recruit participants into the study, as we believed these groups had extensive knowledge of the lived experiences of individuals with TDT. We encouraged these groups to invite diverse interview candidates to ensure that a plurality of voices and experiences was explored. Although data saturation was achieved and several themes were consistently reported, the interview sessions may not represent the lived experiences of all individuals with TDT and their caregivers and the concepts that are important to them. Third, because participation in this research was voluntary, a self-selection bias may have occurred; therefore, the study results may not encompass every concept that is important to individuals living with TDT.

5 Conclusions

Our qualitative analysis demonstrated that individuals living with TDT experience substantial negative impacts on their HRQoL. Conventional treatments are burdensome for these individuals and their caregivers, and some have concerns with the quality of healthcare they receive. Living with TDT significantly affects individuals' physical and psychological well-being, impairing their daily activities and disrupting their family and social life, work, and education. Taken together, our study underscores the unmet needs for alternative treatments for TDT, particularly those that eliminate the necessity of and consequences associated with lifelong RBCTs and ICT. Additionally, there is a necessity for further community HCP education on the impact of TDT and the

importance of offering accessible care for individuals with TDT.

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Declarations

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Conflicts of interest/competing interests Jennifer Drahos, Adriana Boateng-Kuffour, and Nanxin Li are employees of Vertex Pharmaceuticals Incorporated and may hold stock or stock options in the company. Melanie Calvert is the Director of Birmingham Health Partners Centre for Regulatory Science and Innovation and Centre for Patient Reported Outcomes Research and a National Institute for Health and Care Research (NIHR) senior investigator; has received funding from Anthony Nolan, European Regional Development Fund-Demand Hub and Health Data Research UK, Gilead, GlaxoSmithKline, Janssen, Macmillan Cancer Support, Merck, NIHR, NIHR ARC WM, NIHR Birmingham BRC, NIHR BTRU Precision and Cellular Therapeutics, UCB Pharma, UKRI, and UK SPINE; and has received consultancy fees from Aparito, Astellas, CIS Oncology, Daiichi Sankyo, Gilead, Glaukos, GlaxoSmithKline, Halfloop, Merck, Patient-Centered Outcomes Research Institute, Pfizer, Takeda, and Vertex Pharmaceuticals Incorporated. Laurice Levine has received honoraria from Editas and Vertex Pharmaceuticals Incorporated; received consulting fees from Agios and bluebird bio; received support for congress participation from Agios; and has served as an advisory board member for Editas. Neelam Dongha has received consulting fees from Vertex Pharmaceuticals Incorporated. Zahra Pakbaz has received research grants from Amgen, Forma Therapeutics, Global Blood Therapeutics, Novartis, NovoNordisk, and Pfizer; received consulting fees from Agio, Amgen, Dova, Global Blood Therapeutics, Guide point, Novartis, Sanofi, Sobi, and Vertex Pharmaceuticals Incorporated; received honoraria from Cayeene Wellness Center and Child Foundation, Dova, and Global Blood Therapeutics Inc.; served as an advisory board or committee member for Alexion, Sanofi, and Sobi; and acted as a CME course director for the Cayenne Wellness Center and Child Foundation and planning committee member for their annual education symposium. Farrukh Shah has received research grants from IQVIA, Novartis Pharma AG, and Vertex Pharmaceuticals Incorporated; received honoraria from Biologix FZ co, Bristol Myers Squibb, Chiesi Ltd, and Novartis Pharma AG; served as an advisory board or committee member for Agios, bluebird bio, Bristol Myers Squibb, Silence Therapeutics Plc, and Vertex Pharmaceuticals Incorporated; and acted as Chair for the UK Forum on Haemoglobin Disorders. Antony P. Martin is a partner of QC Medica who was funded by Vertex Pharmaceuticals Incorporated to perform this research.

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Consent to participate Not available.

Consent for publication Not available.

Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article and its supplementary information.

Code availability Not available.

Authors' contributions JD, AB-K, and APM were responsible for the study conception and design. APM conducted the interviews and focus group discussions. All authors participated in the data analysis and interpretation and contributed to the writing of the manuscript. All authors were involved in the decision to submit the manuscript for publication and read and approved the final version.

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Authors and Affiliations

Jennifer Drahos[1] · Adriana Boateng-Kuffour[1] · Melanie Calvert[2,3,4,5] · Laurice Levine[6] · Neelam Dongha[7] · Nanxin Li[1] · Zahra Pakbaz[8] · Farrukh Shah[9] · Antony P. Martin[10]

✉ Jennifer Drahos
Jennifer_Drahos@vrtx.com

[1] Vertex Pharmaceuticals Incorporated, 50 Northern Avenue, Boston, MA 02210, USA

[2] Centre for Patient-Reported Outcomes Research, University of Birmingham, Birmingham, UK

[3] National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, UK

[4] NIHR Applied Research Collaboration, West Midlands, University of Birmingham, Birmingham, UK

[5] NIHR Blood and Transplant Research Unit in Precision Transplant and Cellular Therapeutics, University of Birmingham, Birmingham, UK

[6] Orange, CA, USA

[7] London, UK

[8] Division of Hematology Oncology, University of California Irvine School of Medicine, Orange, CA, USA

[9] NHS Blood and Transplant, London, UK

[10] QC Medica, Liverpool, UK